REMARKS

This Preliminary Amendment is filed with a Request for Continuing Examination and a Petition to Revive. The remarks below address the issues raised in the October 24, 2002 Advisory Action. The claims are not amended.

In the Advisory Action, the Examiner states that "there is no reasonable alignment to be made from position 125 to 336 of SEQ ID NO: 74 with the sequence of Chen et al." (page 2, lines 12-13) and takes the lack of homology across this subset of the sequence as evidence that the whole gene is not homologous to the Norrie Disease gene. The Examiner uses this conclusion to reject claims 57-62 under 35. U.S.C. §§101 and 112. Applicants respectfully disagree and traverse.

Applicants respectfully assert that the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. §101. The Federal Circuit has recently stated with respect to the rejection of claims for lack of utility that:

> The PTO cannot make this type of rejection...unless it has reason to doubt the objective truth of the statements contained in the written description. *See In re Brana,* 51 F.3d at 1566, 34 U.S.P.Q.2d at 1441 ("[T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.") (citations omitted); *In re Marzocchi,* 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971)....The PTO may establish a reason to doubt an invention's asserted utility when the written description "suggest[s] an inherently unbelievable undertaking or involve[s] implausible scientific principles." *In re Brana,* 51 F.3d at 1566, 34 U.S.P.Q.2d at 1441; see also *In re Eltgroth,* 419 F.2d 918, 164 U.S.P.Q. 221 (C.C.P.A. 1970) (control of aging process).

In re Cortright, 49 U.S.P.Q.2d 1464, 1466 (C.A.F.C. 1999).

Applicants further note that the "Revised Interim Utility Guidelines Training Materials" ("Utility Guidelines") state that "[t]he Examiner should determine whether any asserted utility is specific and substantial, and if so, why such utility is credible." Utility Guidelines, page 3.

The Utility Guidelines also provide as follows:

> 'Credible utility'—Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong'. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

Utility Guidelines, page 5. The burden is thus on the Examiner to establish, through the presentation of countervailing facts and reasoning, why it is more likely than not that one of ordinary skill in the art would doubt or "question" the truth of the statement of utility.

The Examiner has not provided any evidence that either the logic of Applicants' assertion of utility is seriously flawed or that the facts upon which Applicants base the assertions of utility are inconsistent with the logic underlying those assertions. The Examiner has also not shown how one of ordinary skill in the art would question the Applicants' statement of utility.

It is unclear why the Examiner chooses to focus on only a part of the current invention for the alignment. As is shown in the BLAST data below, a BLAST search of the entirety of SEQ ID NO: 74 shows an 88% identity with the Norrie Disease gene outlined in Chen et al., just as was seen in the alignment that is already of record (Response filed March 18, 2002, Exhibit 1: alignment of pKVC103rB with Human Norrie disease gene), a copy of which is enclosed for the Examiner's reference. A BLAST search of SEQ ID NO: 74 was repeated on July 15, 2003 and is reproduced below as Exhibit 1. The only match is the Chen et al. sequence discussed above.

The Examiner focuses on the fact that part of the sequence, from position 125 to 336, allegedly shows little homology to the Norrie disease gene. Although it is technically true that there is less homology between this part of SEQ ID NO:74 and the Norrie disease gene, it is not precisely true that this lack of homology means that the present invention cannot be a functional equivalent of the Norrie Disease gene.

As attested to in the accompanying Declaration of Dr. Max Cynader, it is well known that complete homology throughout the entire sequence of a gene is not necessary for structural and functional similarities of the encoded protein. The first section of SEQ ID NO:74 is homologous to the Norrie disease gene, suggesting that the protein encoded by the entire

sequence could have similar function to that of the protein encoded by the Norrie gene. The literature concerning the Norrie disease gene does not specify which parts of the sequence encode the parts of the protein that are critical for its functional properties in exacerbating the disease state. For example, it has been shown that extensive deletions in the X chromosome at the locus of the Norrie disease gene lead to a more severe pattern of symptoms (Suarez-Merino et al., *Hum. Mut.* 2001 17(6):523; Hiraoka et al., *J. Hum. Gen.* 2001 46:178). The Chen et al. reference cited by the Examiner also describes deletions in the Norrie Disease gene that nevertheless lead to the disease state. It is thus quite possible that even with only one-third of its sequence homologous to the Norrie gene, the gene encoded by SEQ ID NO:74 still retains enough similarity with the Norrie gene to encode a protein that is functionally identical to the gene referenced by Chen et al.

Dr. Cynader further attests that it is common among a variety of protein families to have homology between critical regions of the DNA sequence but to exhibit substantial divergence among other regions. For example, in the field of ion channels, it is commonly seen that the core group of transmembrane segments of channels specific for potassium are highly homologous not only among different gene products within a species, but across species as well. In contrast, the intracellular and extracellular "tails" of these same proteins show very little homology to one another, although the gene products themselves have very similar functional properties, i.e. they all allow potassium to move from one side of a cell membrane to another. (*Cf.* Rehm and Tempel, *FASEB J.* 1991 Feb; 5(2):164-70; Ponce et al. *J Mem Biol 1997* 159:149) This is analogous to the instant invention, in which it is very possible that the fact that SEQ ID NO:74 is so highly homologous across part of its sequence is an indication that the two gene products will be functionally similar, despite the lack of homology across other parts of its sequence.

Finally, Dr. Cynader points out that SEQ ID NO:74 uniquely aligns with the Norrie Disease gene, and does not show homology with any other genes. This is further evidence that SEQ ID NO:74 is the feline equivalent of the human Norrie Disease gene. Despite the Examiner's reservations concerning the lack of homology between a *subset* of the present invention and the Norrie Disease gene, Applicants respectfully contend that the present invention shows sufficient homology to the Norrie Disease gene to satisfy the requirements for utility as set out in 35 U.S.C. § 101 and enablement under § 112.

Applicants therefore respectfully submit that one of skill, reviewing the relevant percent homologies and alignment information, would conclude that the query sequence (in this case SEQ ID NO:74) is the feline homologue of the subject sequence, in this case the human Norrie Disease gene.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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